

**REMARKS**

Claims 1, 3-6, and 8-25 are pending in the present application. Claim 8 has been amended herein. Upon entry of this amendment, claims 1, 3-6, and 8-25 will be pending in the present application.

Claim 8 has been amended to specify that the isolated nucleic acid hybridizes to at least 10 consecutive nucleotides of a nucleic acid of SEQ ID NO: 1. No new matter is believed to be added by the present amendment, as support can be found throughout the specification (*see, e.g.*, ¶¶ 7, 63).

The citations to the specification included throughout this response are to the paragraph numbers of the published application (US 2004/0157292). Each rejection is addressed individually below.

**I. 35 U.S.C. § 101**

Claims 1, 3-6, and 8-25 were rejected under 35 U.S.C. § 101 as allegedly lacking utility. Applicants respectfully disagree with the rejection.

Claims 1, 3-6, 8, 10, and 11 are directed to CatSper1 nucleic acids, including subsequences of an entire CatSper1 nucleic acid, sequences encoding subsequences of an entire CatSper1 protein, sequences sharing at least 80% identity with a CatSper1 sequence, and sequences capable of hybridizing to a CatSper1 sequence under specified stringency conditions. Claims 9 and 12-25 are all dependent claims.

The Office Action asserts that “no well-established utility exists for newly-isolated complex biological molecules. The specification does not discuss evidence or disclose experiments that impart *any* function for the claimed polynucleotide of SEQ ID NO: 1 in the context of the cell or organism” (Office Action at page 3, second full paragraph) (emphasis in original). The Office Action further states that:

The specification presents data in which the mouse CatSper1 channel of SEQ ID NO: 3 was tested in several assays of sperm motility and function .... Such data have *not* been collected for the claimed nucleic acid of SEQ ID NO: 1 or the polypeptide encoded

by SEQ ID NO: 1. In fact with its low homology to the CATSPER family of genes (31% homology at best), it cannot be determined if the claimed nucleic acid actually even encodes a calcium channel (Office Action at pages 3-4) (emphasis in original).

Applicants respectfully disagree with these assertions.

According to the MPEP, “the Office [is] to presume that a statement of utility made by an applicant is true” (MPEP § 2107.02 III.A at 2100-30 (8<sup>th</sup> Ed., Rev. 7, September 2007), citing *In re Langer*, 503 F.2d 1380, 1391 (C.C.P.A. 1974); *In re Malachovski*, 530 F.2d 1402, 1404 (C.C.P.A. 1976); *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995)). The MPEP further states that:

to overcome the presumption of truth that an assertion of utility by the applicant enjoys, *Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., “question”) the truth of the statement of utility*. The evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration .... A preponderance of the evidence exists when it suggests that it is more likely than not that the assertion in question is true .... This means that if the applicant has presented facts that support the reasoning used in asserting a utility, Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant’s assertion of utility (MPEP § 2107.02 III.A at 2100-30-31) (citations omitted) (emphasis added).

“Office personnel must determine if the assertion of utility is credible .... An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion” (MPEP § 2107.02 III.B at 2100-31) (emphasis in original). Finally, with regard to asserted therapeutic or pharmacologic utility, the MPEP states:

If an applicant provides data, whether from *in vitro* assays or animal tests or both, to support an asserted utility, and an explanation of why that data supports the asserted utility, the Office will determine if the data and the explanation would be viewed by one skilled in the art as being reasonably predictive of the asserted utility .... If the data supplied is consistent with the asserted utility, the Office cannot maintain a rejection under 35 U.S.C. 101.

....

Thus, if one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, evidence from those tests should be considered sufficient to support the credibility of the asserted utility (MPEP § 2107.03 III at 2100-35) (citations omitted).

The specification teaches that CatSper1 is a sperm-specific protein (¶ 37) detected only in testis in screens of human and mouse tissues:

CatSper1 mRNA was detected only in testis when examined in 8 mouse tissues (heart, grain, spleen, lung, liver, skeletal muscle, kidney and testis) and 16 human tissues (pancreas, kidney, skeletal muscle, liver, lung, placenta, brain, heart, spleen, thymus, prostate, ovary, small intestine, colon mucosal lining, peripheral blood leukocytes, and testis). Furthermore, a CatSper1 mRNA probe recognized only testis in a dot blot of 50 human tissue mRNAs (whole brain, amygdala, caudate nucleus, cerebellum, cerebral cortex, frontal lobe, hippocampus, medulla oblongata, occipital lobe, putamen, substantia nigra, temporal lobe, thalamus, nucleus accumbens, spinal cord, heart, aorta, skeletal muscle, colon, bladder, uterus, prostate, stomach, testis, ovary, pancreas, pituitary gland, adrenal gland, thyroid gland, salivary gland, mammary gland, kidney, liver, small intestine, spleen, thymus, peripheral leukocyte, lymph node, bone marrow, appendix, lung, trachea, placenta, fetal brain, fetal heart, fetal kidney, fetal liver, fetal spleen, fetal thymus, fetal lung) (¶ 206; *see also* ¶¶ 207-208).

The specification further discloses that male mice lacking the CatSper1 gene (¶ 210) cannot engender pregnancies (¶ 213). The specification also teaches that in mice, “disruption of the CatSper1 gene resulted in dramatically reduced sperm motility” (¶ 217) and “CatSper1 is required for the sperm to be able to penetrate the ovum outer layers ...” (¶ 220). Finally, comparisons of wild-type and mutant (*i.e.*, CatSper1 *-/-*) sperm show that “CatSper1 is required for the cAMP- and cGMP-induced Ca<sup>2+</sup> influx in sperm” (¶ 225).

Furthermore, the specification discloses that:

Human CatSper1 exhibited a high degree of homology (55% identity/72% similarity) with its mouse counterpart, especially in the transmembrane domains and the histidine-rich region. In the transmembrane domains there was 81% identity/93% similarity and in the pore region, 89% identity/100% similarity. Low stringency screening of a mouse testis cDNA library with human

CatSper1 revealed no other genes of higher similarity (¶ 204, last three sentences).

In summary, CatSper1 is a sperm-specific protein found in both human and mouse sperm cells (¶¶ 206-208). Male mice lacking the CatSper1 gene cannot engender pregnancies (¶ 213), and their sperm have dramatically decreased motility (¶ 217) and are unable to penetrate the outer layers of the ovum (¶¶ 219-220). Human and mouse CatSper1 exhibit a high degree of similarity and identity, especially in the transmembrane domains and the pore region.

Based on this disclosure, one of skill in the art would appreciate that human CatSper1 can be used to identify molecules that inhibit human CatSper1 expression or activity for use as male and female contraceptives (¶¶ 33, 118). Alternatively, human CatSper1 can be used to identify molecules that enhance human CatSper1 expression or activity to treat infertility (¶ 134). Such molecules could act upon the entire protein, or fragments of the protein (¶¶ 115, 118, 135). "Such fragments include the structural domains of the human CatSper1 proteins, including the transmembrane, loop and pore-forming regions of the proteins ... as well as allelic variants and homologs thereof. CatSper1 fragments include potentially useful epitopes of the CatSper1 proteins" (¶ 100). Examples of contraceptive molecules include small molecules, antisense molecules, antibodies, and antibody fragments (¶ 118). Additionally, human CatSper1 can be used to generate antibodies or other probes for diagnostic uses (¶¶ 17, 18, 21, 62, 69, 109, 111, 125).

The scientific literature published after the filing of the instant application supports the assertion that one of skill in the art would appreciate the utility of the present claims. One group wrote:

Recently, the search for the calcium channels residing in sperm led to the cloning and characterization of a novel gene, named CatSper, which codes for a unique cation channel (Ren *et al.*, 2001) .... *Comparison of human and mouse CatSper amino acid sequences reveals a high degree of conservation, suggesting its critical function throughout evolution.* Deletion of the CatSper gene in mouse revealed its vital role in sperm motility and male fertility. Although CatSper  $-/-$  mice display sexual behaviours that are indistinguishable from wild-type mice, they are infertile. In-depth examination revealed no apparent abnormalities in these mice except for a lack of sperm motility (Ren *et al.*, 2001).

In the present study, we have evaluated the temporal pattern of CatSper gene expression during mouse testis development. Using semi-quantitative RT-PCR, we have also compared the level of CatSper gene expression in two groups of subfertile men to assess any potential abnormality linked to sperm motility. (Nikpoor *et al.*, *Hum. Reprod.* 19(1):124-8 (2004) at page 125, col. 1 (emphasis added) (Exhibit A) ("Nikpoor *et al.*.").

Using human testicular biopsies (Exhibit A at page 126, col. 2, first paragraph), Nikpoor *et al.* compared:

CatSper gene expression in subfertile patients with deficient sperm motility to that of subfertile or fertile patients with motile sperm .... Gene expression levels were examined by semi-quantitative RT-PCR ...., statistical analysis comparing the means between the two groups (Student's *t*-test) revealed a significant difference in the level of hCatSper gene expression ( $P = 0.009$ ) (Exhibit A at page 126, col. 1, last paragraph through page 127, col. 1., first paragraph).

Notably, Nikpoor *et al.* used short sequences of consecutive nucleotides from the CatSper sequence to study male infertility and found a correlation, as described in the instant application.

Nikpoor *et al.* concluded "[o]ur results showed that CatSper gene expression was significantly reduced in these patients [with deficient sperm motility] as compared with controls. This finding *provides clinical confirmation* of conclusions drawn in the original report by Ren *et al.* (2001), linking CatSper gene expression to sperm motility and male fertility" (Exhibit A at page 128, col. 1, first full paragraph (emphasis added)), and that "[t]he data obtained in this study support a potential role for CatSper in sperm motility and fertility in mouse and human. *CatSper is therefore implicated as a potential target* to explore the molecular mechanisms of male infertility" (Exhibit A at abstract (emphasis added)).

A review article titled "Sperm Ion Channels: Molecular Targets for the Next Generation of Contraceptive Medicines?" stated "that *selective CatSper1 inhibitors may attenuate or curtail sperm motility and consequently impair fertilization*. The restricted localization of CatSper1 in mature sperm implies that a selective blocker should not affect other tissues, thus minimizing any potential side effects. This notion is supported by the normal development and behavior of the mutant mice (Ren *et al.*, 2001)" (Zhang and Gopalakrishnan, *J. Androl.*

26(6):643-53 (2005) at page 649, col. 2, first full paragraph (emphasis added) (Exhibit B) (“Zhang”). Zhang also stated that “the critical roles revealed for the members of the CatSper family of proteins in sperm hyperactivated motility endow these proteins *as likely drug targets* ...” (Exhibit B at page 651, cols. 1-2 (emphasis added)).

Applicants respectfully note that they are both authors of Ren *et al.*, *Nature* 413(6856):603-609 (2001)(Exhibit C) cited in Exhibits A and B, and that the instant application is based in part on that publication (*compare* Exhibit C with Examples 1-7 at ¶¶ 202-225). Therefore, Applicants’ present disclosure led at least two groups of skilled artisans to conclude that CatSper1 is a target for human contraception (*see* Exhibits A and B). Applicants’ present disclosure of mouse and human data also led one group to perform a human clinical trial, which verified the link between human CatSper1 expression and sperm motility (*see* Exhibit A). Thus it *cannot* be “establish[ed] that it is more likely than not that one of ordinary skill in the art would doubt (*i.e.*, ‘question’) the truth of the statement of utility” as required by MPEP § 2107.02 III.A.

Accordingly, Applicants respectfully submit that the specification provides sufficient disclosure for one of skill in the art to understand that the claimed human CatSper1 sequences have specific and credible utilities as disclosed and claimed in the instant application.

Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be reconsidered and withdrawn.

## II. 35 U.S.C. § 112, First Paragraph – Enablement

Claims 1, 3-6 and 8-25 were rejected for alleged lack of enablement because:

Applicants have neither made fragments of SEQ ID NO: 1, nor confirmed their function. Even if there were a patentable use for the claimed full-length polynucleotide (SEQ ID NO: 1), the claimed variants would not be enabled because the specification has not taught one of ordinary skill in the art how to use them (Office Action at page 5, first full paragraph).

Applicants respectfully disagree with this rejection.

Claims 1, 3-6, 8, and 10-11 and dependent claims 9 and 12-25 are described above.

Applicants respectfully submit that this rejection should be reconsidered and withdrawn for the same reasons stated above with respect to the rejection under 35 U.S.C. § 101.

Specifically, Applicants submit that the application does, in fact, assert multiple specific and credible utilities for the claimed invention and that those of skill in the art would have no difficulty in using the claimed nucleic acids, kits, vectors and cells for the stated purposes.

For example, the CatSper1 protein is a clear target for the development of male contraceptives or diagnosis of male infertility. As explained in detail in the working examples provided in the specification, CatSper1 knock-out mice were produced (Example 3) and demonstrated an inability to engender pregnancies (Example 4), “dramatically reduced sperm motility” (Example 5), and the sperm were unable to fertilize eggs (Example 6). Furthermore, “Human CatSper1 exhibited a high degree of homology (55% identity/72% similarity) with its mouse counterpart, especially in the transmembrane domains and the histidine-rich region ... [and] in the pore region, 89% identity/100% similarity” (¶ 209).

Therefore, the CatSper1 nucleic acids have utility in producing animal models of human male fertility and infertility, in producing transformed cells expressing CatSper1 to screen for inhibitors of CatSper1 activity, for RNA expression profiling of human sperm to identify abnormalities of CatSper1 expression, for genetic testing of humans to identify mutations of CatSper1 responsible for infertility, and the like. Moreover, fragments of the complete coding sequence (e.g., those encoding polypeptides likely to be antigenic, those encoding functional domains, and those likely to represent unique sequences in the genome) have clear utilities to those of skill in the art (e.g., developing anti-CatSper1 antibodies, screening for ligands in affinity assays, isolating CatSper1 sequences from genomic or cDNA samples). These and other utilities are described at length in the specification. Exhibits A and B verify that one of skill in the art would appreciate these utilities and can understand how to use the claimed subject matter.

Furthermore, fragments of at least 10-18 consecutive bases can be used as probes or primers to detect the presence of CatSper1. Each nucleotide in a sequence may be one of four bases. Thus a fragment of 10 consecutive bases is one of  $4^{10}$  possibilities, or one in 1,048,576. A fragment of 18 consecutive bases is one of  $4^{18}$  possibilities, or one in 68,719,476,736. Therefore, a specific fragment of 10-18 consecutive bases has a less than a one in a million chance of occurring randomly. Accordingly, a probe or primer directed to a specific fragment of

10-18 consecutive bases is highly likely to identify the molecule of interest. In the instant case, a probe or primer directed to a specific fragment of 10-18 consecutive bases of SEQ ID NO: 1 is highly likely to detect the presence of CatSper1.

Applicants respectfully submit that, given the substantial demonstration of CatSper1's critical role in sperm motility and fertility, both in the instant specification and in the literature, the utility of the claimed invention is as clear as that for any pharmaceutical target, and that the patentability of pharmaceutical targets has been unquestioned for decades. Accordingly, one of skill in the art could, based upon the disclosure of the specification, produce transformed cell lines (¶¶ 78-82), transgenic animals (¶¶ 84-96, 210), substantially pure CatSper 1 proteins and polypeptides (¶¶ 98-102), antibodies (¶¶ 104-111), and assays to identify modulators of CatSper 1 expression or activity (¶¶ 113-115).

Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

### **III. 35 U.S.C. § 112, First Paragraph – Written Description**

Claims 1, 3-6, 8, 10, and 11 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not describe the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention. Applicants respectfully disagree.

Claims 1, 3-6, 8, 10 and 11 are described above.

The Office Action asserts that:

Applicants have neither made nor used any variants of SEQ ID NO: 1 or its encoded polypeptide. Since there was no reduction to practice to support the claim language, applicants were therefore not in possession of all or a significant number of variants of SEQ ID NO: 1 which *retain the function* of SEQ ID NO: 1 ....  
[A]dequate written description requires more than a mere statement that a fragment or variant is part of the invention and that one of skill in the art could easily make such fragments and variants (Office Action at page 6) (emphasis in original).

As an initial matter, Applicants submit that they were clearly in possession of the complete CatSper1 nucleic acid and protein sequences. As such, Applicants submit that those of skill in the art would recognize that they were clearly in possession of subsequences as recited in claim 1.

Furthermore, the specification teaches that “subsets of the CatSper1 nucleic acid sequences are provided for use as primers for nucleic acid amplification reactions, as probes in hybridization assays to detect CatSper1 sequences in samples of other nucleic acids, or as probes to distinguish normal or wild-type sequence from abnormal or mutant sequences” (¶ 63). Therefore, these fragments possess utility even if they do not “*retain the function* of SEQ ID NO: 1.” Although Applicants may not have actually reduced to practice all such primers and probes, the filing of the instant application serves as a constructive reduction to practice (MPEP § 2138.05 at 2100-109, col. 1, second paragraph). “[T]he inventor need not provide evidence of either conception or actual reduction to practice when relying on the content of the patent application” (*id.*).

Figure 1A clearly shows an entire CatSper1 sequence and delineates the positions of the transmembrane, loop and pore regions. The specification also provides a list of sequences having high predicted antigenicity. Therefore, Applicants submit that those of skill would clearly recognize that Applicants were in possession of the nucleic acids as recited in claims 3 and 4.

Given the complete CatSper1 nucleic acid sequence, one of skill in the art can clearly identify sequences with 80% identity to that sequence, or any subsequence thereof. Therefore, Applicants submit that those of skill would clearly recognize that Applicants were in possession of the nucleic acids as recited in claim 5.

Given the complete CatSper1 nucleic acid sequence, and the experiments disclosed in the specification for detecting CatSper1 activity, one of skill in the art can clearly identify sequences with 80% identity to that sequence and retain the activity. Therefore, Applicants submit that those of skill would clearly recognize that Applicants were in possession of the nucleic acids as recited in claim 6.

DNA hybridization experiments were well within the ability of those of skill in the art, at the time of filing. Given the complete CatSper1 nucleic acid sequence, and such routine skill, one of skill in the art can clearly identify sequences that hybridize under specified conditions. Therefore, Applicants submit that those of skill would clearly recognize that Applicants were in possession of the nucleic acids as recited in claim 8.

Finally, with respect to claims 10 and 11, which substantially include the limitations of claims 6 and 8 discussed above, one of skill in the art, particularly in view of the teachings of the specification, can clearly produce the claimed operably joined sequences. Therefore, Applicants submit that those of skill would clearly recognize that Applicants were in possession of the nucleic acids as recited in claims 10 and 11.

For the foregoing reasons, Applicants respectfully request that the rejections of claims 1, 3-6, 8, 10, and 11 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

#### **IV. 35 U.S.C. § 102(b)**

Claims 8, 10, and 12 were rejected under 35 U.S.C. § 102(b) for alleged anticipation in view of Sanger Centre (1998, Science, 282:2012-2018, Accession No. Z82256.1) (“the Sanger Centre sequence”). The Office Action states:

The Sanger Centre Consortium disclosed a polynucleotide sequence encoding a nematode sodium channel which is 29% identical to SEQ ID NO: 1 in the instant application. There are several short identical areas where the nucleotides are the same, such as in the region of residues 174-181. This reference meets the limitations of claims 8, 10, and 12 because “a portion” of SEQ ID NO: 1 can be a very short segment, even just one or a few bases.

(Office Action at page 8, first paragraph) (emphasis added).

Amended claim 8 recites an isolated nucleotide sequence that hybridizes to at least 10 consecutive nucleotides of SEQ ID NO: 1 under specific conditions. Claim 10 recites a nucleotide sequence encoding a polypeptide having CatSper1 activity and that hybridizes to a portion of SEQ ID NO: 1 under specific conditions. Claim 12 recites a kit for detecting at least a

portion of a CatSper1 nucleic acid comprising an isolated nucleic acid of any one of claims 1, 3-6, and 8-11.

Amended claim 8 requires that the isolated nucleic acid hybridizes to at least 10 consecutive nucleic acids of SEQ ID NO: 1. The region of the Sanger Centre sequence cited in the Office Action (*i.e.*, residues 174-181) has only 8 consecutive nucleic acids of SEQ ID NO: 1. Therefore, that region of the Sanger Centre sequence does not disclose “each and every element” of amended claim 8 as required by § 102(b).

The Office Action provides no evidence that the Sanger Centre sequence has CatSper1 activity as recited in claim 10 and, therefore, the Sanger Centre sequence does not disclose “each and every element” of claim 10 as required by § 102(b).

Claim 12 recites a kit including a CatSper1 nucleic acid and means for detecting said nucleic acid. The Sanger Centre sequence discloses neither a kit nor means for detecting a nucleic acid. Therefore, the Sanger Centre sequence does not possess “each and every element” of claim 12 as required by § 102(b).

Therefore, Applicants respectfully request that the rejection of claims 8, 10, and 12 under 35 U.S.C. § 102 be reconsidered and withdrawn.

### **CONCLUSION**

In view of the amendment and arguments made herein, Applicants respectfully request reconsideration of all claims, and submit that the claims are in condition for allowance.

No fees are believed to be due with this Response. However, if such a fee is due or a credit is owed, please make them to our Deposit Account No. 08-0219, referencing Attorney Docket No. 0110313.135US3.

Respectfully submitted,

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